

AMENDMENT

Attorney Docket No.: Q64929

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cont

figure correspond to the clinical data of the intravenous injection of pamidronate (90 mg/4 weeks) (Lipton, A., Eur. J. Cancer, Vol. 34, 2021, 1998).

REMARKS

Minor amendments which clarify the specification, without introduction of new matter, are set forth. Entry and consideration of this Amendment is respectfully requested.

Respectfully submitted,

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The specification is changed as follows:

Pages 2-3, First full paragraph:

In treating multiple myeloma, use is mainly made of chemotherapies (MP therapy, VAD therapy, C-VAD therapy, polypharmacy, etc.) and chemotherapy with the use of IFN- α . Also, topical radiotherapy and the like are selected depending on the bone lesion conditions (*ibid.*, Clinical Oncology, edited by Japan Clinical Oncology Group, published in 1996 by Gan to Kagakuryoho Sha). As the results of the long-term observation on patients with multiple myeloma under chemotherapy, it is reported that a bone resorption marker in urine did not correlate to changes in M proteins due to chemotherapy in many cases, though a tendency toward a decrease in the bone resorption marker was observed in a chemotherapy reaction group showing a decrease of 25% or more in M proteins (Blood, 90, 3743-3750, 1997). Therefore, it becomes more and more necessary to establish a novel therapy for bone lesions accompanying multiple myeloma from the viewpoint of patients' QOL.

Pages 4-5, First full paragraph:

Recently, studies have been made on the anticancer effects of BP's and it is reported that several BP's have an effect of inhibiting cell proliferation *in vitro* (British J. Haematology, 98, 665-672, 1997), though any clinical usefulness has been proved in none of these cases and some reports rather denying the anticancer effect of BPs are also presented. That is to say, it is reported that pamidronate has been used in a murine model of myeloma, and

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although no effect on tumor growth was demonstrated, there was evidence of a cytotoxic effect within the bone marrow. It is also reported that risedronate has been used in a murine model of myeloma; however, although there was a clear reduction in bone destruction, no effect on tumor burden was noted (Leukemia and Lymphoma, 32, 129-138, 1998). In a patient who was intravenously administered in a higher dose than in prior clinical studies, a transient decrease in a cancer marker was observed. However, it is reported that it is possible that for a cytostatic or even cytotoxic effect to occur, higher dose or more frequent administration of pamidronate is required compared to dosing for its beneficial bone effects (British J. Haematology, 103, 530-532, 1998). Accordingly, it has never been reported hitherto that BPs exert an anticancer effect (i.e., a therapeutic effect on multiple myeloma) in patients with multiple myeloma.

Page 14, First and Second full paragraph:

In case of usual oral administration, the daily dose ranges from about 1 to 20 mg, preferably from about 3 to 10 mg and still preferably from about 6 to 9 mg/kg. The daily dose is administered once a day or divided into 2 to 4 doses per day. The dose may be appropriately determined case by case taking the body weight, conditions, age, sex, etc. of the patient into consideration.

In case of intravenous administration, the single dose ranges from about 0.1 to 10 mg, preferably from about 0.1 to 5 mg and still preferably from about 0.5 to 2 mg/kg. The composition can be intravenously dripped in this dose once in 2 to 6 weeks, preferably once in 3 to 5 weeks and still preferably once in 4 weeks over 10 to 60 minutes (preferably 30 minutes). The dose may be appropriately determined case by case taking the body weight, conditions, age, sex, etc. of the patient into consideration.

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Page 15, First full paragraph:

Fig. 1 is a diagram which shows the bone resorption inhibition level with the use of urinary deoxypyridinoline level as a marker. Each column in this figure represents mean \pm standard error. Number of mice is indicated in columns. Comparisons with the sham-operated group and the solvent group with paralysis in hind limb were performed with the Student's t-test.

* significantly different from the solvent group with paralysis in hind limb. (**: Dunnett's multiple range test, $p<0.01$).

Page 15, Third full paragraph:

Fig. 3 shows changes in urinary Dpyr level (a bone resorption marker) in 4 weeks after the oral administration of the compound A (6 mg/day) in Example 5. In this figure, the abscissa indicates time (weeks) after the start of the administration, while the ordinate indicates the Dpyr level referring the Dpyr level before the administration as to 100%. The pamidronate data in this figure correspond to the clinical data of the intravenous injection of pamidronate (90 mg/4 weeks) (Lipton, A., Eur. J. Cancer, Vol. 34, 2021, 1998).

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